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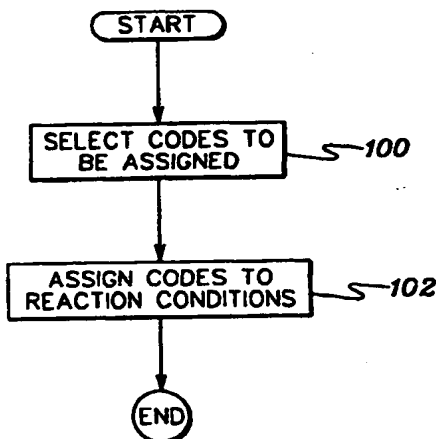
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(54) Title: SELECTING CODES TO BE USED FOR ENCODING COMBINATORIAL LIBRARIES



(57) Abstract

Codes to be used for encoding combinatorial libraries are selectively chosen based on one or more predefined function or criterion. In particular, a subset of N possible codes is selected based on some criterion. In one example, the codes are binary codes, and each code represents the tags used during a particular stage of synthesis of members of a combinatorial library. The tags define the reaction condition used during that particular stage of synthesis. In one embodiment, the predefined criterion ensures that each code includes more than one tag. This helps eliminate ambiguity during a decoding process in which the tags are identified to determine the reaction history during synthesis.

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## SELECTING CODES TO BE USED FOR ENCODING COMBINATORIAL LIBRARIES

### TECHNICAL FIELD

This invention relates, in general, to the encoding of combinatorial libraries  
5 and, in particular, to selectively choosing codes to be assigned to reaction  
conditions used during synthesis of a combinatorial library.

### BACKGROUND ART

Combinatorial techniques of chemical synthesis allow the creation of  
molecular libraries having immense diversity. These techniques entail a series of  
10 chemical steps with multiple choices of reaction conditions (e.g., reagents,  
temperature changes, etc.) for each step. The complexity, or number of members  
in a combinatorial library, is given by the product of the number of reaction  
conditions for each step of the synthesis, and can therefore, be quite large. The  
challenge in using combinatorial libraries is the characterization of members of the  
15 library with particular desired properties.

One solution to the above challenge is to use a split synthesis or direct  
divide technique to perform chemical synthesis on solid particles, such as beads.  
Through a protocol of separating and mixing beads during the synthesis, each bead  
in the final library has a product from a single, specific reaction sequence  
20 chemically bound to it, and that product is likely to differ from that bound to  
another bead.

During each step of the synthesis, zero or more tags (e.g., tagging  
molecules) are attached to each bead in order to encode the reaction condition  
used in that step, as well as the step number.

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In one embodiment, the tags are used in combination with one another to form a binary record of the synthetic steps for each bead. For example, assume a combinatorial synthesis using any of seven different reagents in each of N steps is to be carried out. Such a combinatorial synthesis would yield  $7^N$  different final products. As an example, the various reagents which can be used in any step are designated as binary 001(Reagent 1), 010(Reagent 2), 011(Reagent 3),... 111(Reagent 7). Thus, a binary synthesis code describing any complete N-STEP synthesis using  $3 \times N$  binary digits can be written.

For instance, if Reagent 3 is used in the first step, the binary numerical description is 011. If Reagent 1 is used in the second step, the description is 001 011. Further, if Reagent 6 is used in the third step, the description is 110 001 011. This 9-bit binary synthesis code describes the synthesis, and can be read from right to left in 3-bit blocks to decode the reagents used in each step of the synthesis.

To represent such a synthesis code chemically, a set of distinguishable, sensitively detectable molecules is used as tags, and the presence of a particular tag represents a binary "1" for the corresponding bit. Using a set of nine tagging molecules, T9-T1, for the above example, where T9 represents the leftmost binary bit and T1 represents the rightmost bit, the tag mixture containing only T9, T8, T4, T2 and T1 represents the 110 001 011 synthesis code.

The use of tags and various encoding techniques are described in detail in one or more of the following references, each of which is hereby incorporated herein by reference in its entirety: Ohlmeyer et al., "Complex synthetic chemical libraries indexed with molecular tags", Proceedings Of The National Academy Of Sciences Of The United States Of America, Vol. 90, No. 23, pp. 10922-10926 (December 1993); J.J. Baldwin, "Design, synthesis and use of binary encoded synthetic chemical libraries", Molecular Diversity, Vol. 2, No. 1/2, pp. 81-88 (October 1996); Burbaum et al., "A paradigm for drug discovery employing encoded combinatorial libraries", Proceedings Of The National Academy Of

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Sciences Of The United States Of America, Vol. 92, No. 13, pp. 6027-6031 (June 1995); Still et al., U.S. Patent No. 5,565,324, entitled "Complex Combinatorial Chemical Libraries Encoded With Tags", issued on October 15, 1996; Baldwin et al., U.S. Patent No. 5,618,825, entitled "Combinatorial Sulfonamide Library",  
5 issued on April 08, 1997; Baldwin et al., U.S. Patent No. 5,663,046, entitled "Synthesis Of Combinatorial Libraries", issued on September 02, 1997; Still et al., International Publication No. WO 94/08051, entitled "Complex Combinatorial Chemical Libraries Encoded With Tags", International Publication Date April 14, 1994; Dower et al., U.S. Patent No. 5,639,603, entitled "Synthesizing And  
10 Screening Molecular Diversity", issued on June 17, 1997; and Dower et al., International Publication No. WO 93/06121, entitled "Method Of Synthesizing Diverse Collections Of Oligomers", International Publication Date April 01, 1993.

While binary coding has been established as a viable technique in encoding complex combinatorial libraries, there are some shortcomings with the present  
15 techniques, especially during decoding of the tags.

Decoding is performed in order to determine the reaction history of a particular bead. In particular, during decoding, any tag(s) attached to a bead is detached and identified to determine the particular conditions that occurred during synthesis. One technique for separating and identifying tags is known as Capillary  
20 Gas Chromatography (GC).

During decoding, it is sometimes difficult to determine whether a tag is present due to impurities of similar retention times or tags present in low amounts. Thus, the decoding becomes ambiguous, and it is difficult, under those circumstances, to determine the appropriate binary code that represents the  
25 reaction history.

Based on the foregoing, a need exists for a coding technique that eliminates ambiguous code reading. A further need exists for a capability that

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enables the selective choosing of codes, from N possible codes, to be assigned to reaction conditions. A yet further need exists for a capability that guarantees the presence of enough tag peaks in a chromatogram that, even in the presence of significant variability in the absolute timing of the run, the relative timing can be determined. That is, a need exists for the presence of at least two tag peaks, so that the time distance (i.e., relative timing) between those peaks can be determined, even if there is significant variability in their positions (i.e., absolute timing). A further need exists for a capability that uses this time distance to confirm whether a particular peak represents the presence of a tag or a contaminant (e.g., substantially constant time spacing indicates the presence of a tag). The use of time spacing as a confirmation of whether a peak represents a tag or a contaminant is referred to herein as "self-clocking".

#### SUMMARY OF THE INVENTION

The shortcomings of the prior art are overcome and additional advantages are provided through the provision of a method of determining codes usable in encoding combinatorial libraries. The method includes, for instance, selecting a plurality of codes to be assigned to a plurality of reaction conditions usable during synthesis of a combinatorial library. Each of the plurality of codes includes a plurality of tags, wherein none of the plurality of codes includes only a single tag. The method further includes assigning selected codes to reaction conditions.

In one embodiment, each of the plurality of codes is a binary code, and a binary "one" within the binary code represents the presence of a particular tag.

In another embodiment of the invention, the plurality of codes is selected using a predefined criterion. The predefined criterion specifies at least one of the following: each of the plurality of codes includes an even number of tags present therein; each of the plurality of codes includes an odd number of tags present therein; each of the plurality of codes includes up to a maximal number of tags

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present therein; each of the plurality of codes includes up to a maximal number of "zero" bits; and each of the plurality of codes does not include a predetermined pattern of bits.

In another embodiment, the plurality of codes is selected using a parity bit.

5           In a further aspect of the present invention, a method of determining codes usable in encoding chemical libraries is provided. The method includes selecting, from N possible codes, a group of codes to be assigned to a plurality of reaction conditions usable during synthesis of a chemical library. The selecting includes using a predefined function to select the group of codes, wherein the predefined  
10       function selects fewer than N-1 codes from the N possible codes. The method further includes assigning selected codes to reaction conditions.

          In yet a further aspect of the present invention, a method of determining codes usable in encoding chemical libraries is provided. The method includes selecting, from N possible codes, a plurality of codes to be assigned to a plurality  
15       of reaction conditions, wherein the plurality of codes satisfies a predefined criterion. The predefined criterion is other than excluding an "all zeroes" code. The method further includes assigning selected codes to reaction conditions.

          In a further aspect of the present invention, a system of determining codes  
20       usable in encoding combinatorial libraries is provided. The system includes means for selecting a plurality of codes to be assigned to a plurality of reaction conditions, in which each of the plurality of codes includes a plurality of tags, such that none of the plurality of codes includes only a single tag. The system further includes means for assigning selected codes to reaction conditions.

25           In another aspect of the present invention, a system of determining codes usable in encoding chemical libraries is provided. The system includes means for selecting, from N possible codes, a group of codes to be assigned to a plurality of

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reaction conditions usable during synthesis of a chemical library. The means for selecting includes means for using a predefined function to select the group of codes, wherein the predefined function selects fewer than N-1 codes from the N possible codes. The system further includes means for assigning selected codes to  
5 reaction conditions.

In yet a further aspect of the present invention, a system of determining codes usable in encoding chemical libraries is provided. The system includes means for selecting, from N possible codes, a plurality of codes to be assigned to a  
10 plurality of reaction conditions, wherein the plurality of codes satisfies a predefined criterion, wherein the predefined criterion is other than excluding an "all zeroes" code. The system further includes means for assigning selected codes to reaction conditions.

In another aspect of the present invention, an article of manufacture is  
15 provided, including at least one computer usable medium having computer readable program code means embodied therein for causing the determining of codes usable in encoding combinatorial libraries. The computer readable program code means includes computer readable program code means for causing a computer to select a plurality of codes to be assigned to a plurality of reaction  
20 conditions usable during synthesis of a combinatorial library, each of the plurality of codes including a plurality of tags, wherein none of the plurality of codes includes only a single tag; and computer readable program code means for causing a computer to assign selected codes to reaction conditions.

In yet another aspect of the present invention, at least one program storage  
25 device is provided, which is readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of determining codes usable in encoding chemical libraries. The method includes selecting, from N possible codes, a group of codes to be assigned to a plurality of reaction conditions usable during synthesis of a chemical library. The selecting



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includes using a predefined function to select the group of codes, wherein the predefined function selects fewer than N-1 codes from the N possible codes. The method further includes assigning selected codes to reaction conditions.

5 In a further aspect of the present invention, at least one program storage device is provided, which is readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of determining codes usable in encoding chemical libraries. The method includes selecting, from N possible codes, a plurality of codes to be assigned to a plurality of reaction conditions, wherein the plurality of codes satisfies a predefined  
10 criterion. The predefined criterion is other than excluding an "all zeroes" code. The method further includes assigning selected codes to reaction conditions.

In accordance with the principles of the present invention, a coding capability is provided that eliminates ambiguous code reading. Further, the  
15 capability of the present invention advantageously enables the selective choosing of codes, from N possible codes, to be assigned to reaction conditions. Further, the capability of the present invention guarantees the presence of enough tag peaks in a chromatogram that, even in the presence of significant variability in the absolute timing of the run, the relative timing can be determined. Additionally, the  
20 present invention is advantageously self-clocking. The use of the present invention in each synthesis step can result in the avoidance of single bit codes for reaction conditions.

Additional features and advantages are realized through the techniques of the present invention. Other embodiments and aspects of the invention are  
25 described in detail herein and are considered a part of the claimed invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

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The subject matter which is regarded as the invention is particularly pointed out and distinctly claimed in the claims at the conclusion of the specification. The foregoing and other objects, features, and advantages of the invention will be apparent from the following detailed description taken in  
5 conjunction with the accompanying drawings in which:

FIG. 1 depicts a generalized method of the present invention;

FIG. 2 depicts one embodiment of the logic associated with the selection capability of the present invention;

10 FIG. 3 depicts one example of N possible codes, in which a subset is selected (or "accepted") therefrom, in accordance with the principles of the present invention;

FIG. 4 depicts one example of a table of accepted codes, in accordance with the principles of the present invention;

15 FIG. 5 depicts one embodiment of the table of accepted codes of FIG. 4, in which the codes are assigned to reaction conditions, in accordance with the principles of the present invention;

FIG. 6 depicts another example of accepted codes, in accordance with the principles of the present invention;

20 FIG. 7a depicts another example of N possible codes, in which a subset is selected (or accepted) therefrom, in accordance with the principles of the present invention;

FIG. 7b depicts one example of adding a parity bit to the N possible codes of FIG. 7a in order to make a selection of the codes to be

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included in the subset of accepted codes, in accordance with the principles of the present invention;

FIG. 8 depicts one example in which it is difficult to determine whether a tag is present in a sample;

5           FIG. 9 illustrates one example of output from a gas chromatograph, in accordance with the principles of the present invention;

FIG. 10 depicts another example of output from a gas chromatograph, in accordance with the principles of the present invention; and

10           FIG. 11 depicts one embodiment of a computer environment providing and/or using the capability of the present invention.

### BEST MODE FOR CARRYING OUT THE INVENTION

In accordance with the principles of the present invention, a capability is provided in which codes to be assigned to reaction conditions are selectively  
15   chosen based on one or more criterion. That is, out of N possible codes, a subset of the N codes is selected based on some constraint or some predefined function.

The codes are, for instance, binary codes, and each code represents the tags used during a particular stage of synthesis of members of a combinatorial library. Specifically, the tags define the reaction condition used during that  
20   particular stage of synthesis.

A generalized technique of one embodiment of the present invention is described with reference to FIG. 1. Initially, a group of acceptable codes is selectively chosen, from N possible codes, based upon a predefined function or

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one or more criterion, as described in detail below, STEP 100. Thereafter, the selected codes are assigned to reaction conditions, and those conditions may be used during synthesis of library members, STEP 102. The assignment may be arbitrary or may be based on one or more factors. For instance, the first code may  
5 be assigned to the first condition to be used during synthesis, etc.

One embodiment of the selection process used to choose a group of codes to be assigned to the reaction conditions is described in detail with reference to FIG. 2. Initially, a decision is made as to the N possible codes that could be used for a particular synthesis step, STEP 200. For example, a determination is made  
10 as to how many bits are sufficient to represent the number of reaction conditions to be used during that step. Assume for this one example that four bits are sufficient. Thus, in a binary scheme, there are  $2^4$  possible codes (i.e., N=16), as shown in FIG. 3.

Out of the possible codes, only those codes that satisfy one or more  
15 criterion (or predefined function) are selected. The criterion can include many different possibilities. As examples, the criterion can select codes having an even number of "one" bits (i.e., an even number of tags); an odd number of "one" bits; an odd number, greater than one, of "one" bits; more than one tag (i.e., more than one binary "one" bit); up to a total number of "zero" bits; up to a total number of  
20 "one" bits; up to a maximal allowed sequence of "zero" or "one" bits; an even parity; an odd parity; codes that do not include a predefined sequence of bits (e.g., the codes that do not include a sequence of 101), etc. The above criteria are only provided as examples. There are many more possibilities, and each of those possibilities is considered a part of the claimed invention.

25 For illustration purposes only, the predefined function, in this example, includes all those codes that have up to a total of two "zeroes". Thus, the process continues with determining which of the codes of FIG. 3 meet this criterion.

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Returning to FIG. 2, a code is considered from the possible codes, STEP 202. For example, code 0000 is considered from the codes depicted in FIG. 3. A determination is made as to whether the considered code meets the criterion of having no more than two zeroes, STEP 204. Since code 0000 has more than two zeroes, it does not meet the criterion, and thus, is not an acceptable code. Therefore, if there are further codes to be considered, INQUIRY 206, a new code is considered, STEP 202.

Proceeding sequentially down the list of the possible codes illustrated in FIG. 3, the next code is 0001. Again, since code 0001 does not meet the criterion, STEP 204, and there are more codes, INQUIRY 206, another code is selected. This procedure continues. At some point, a code is selected that does meet the criterion, INQUIRY 204. For instance, code 0011 meets the criterion of having at a maximum two "zeroes", thus, this code is selected as an acceptable code.

In one example, the acceptable code is placed in a table of acceptable codes, STEP 208. One instance of such a table is depicted in FIG. 4. The above process continues until all of the acceptable codes are selected from the possible codes based on the predefined criterion.

As described with reference to FIG. 1, after the acceptable codes are determined, each of the acceptable codes can be assigned, respectively, to one of a plurality of reaction conditions, as depicted in FIG. 5. In this particular case, ten reaction conditions are represented by ten unique codes.

Another example of a predefined function used to select acceptable codes from N possible codes is one in which all codes having an even number of tags is selected. This is depicted in FIG. 6. In this particular example, five bits are considered necessary to represent the various reaction conditions to be used during synthesis. Thus, there are 32 possible codes. Out of the 32 possible codes,

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15 codes are acceptable (designated by "used" in the table). That is, 15 codes meet the criterion of having an even number of tags.

5 In yet another embodiment of the present invention, parity bits may be added to the N possible codes in order to determine the acceptable codes. For example, assume there are eight possible codes, as shown in FIG. 7a. Further, assume that even parity is to be used, in this example. Thus, for each code in which the addition of a binary "one" provides an even number of "one" bits, a parity "one" bit is added, as shown in FIG. 7b.

10 Thereafter, the codes having the parity "one" bit are selected from the N possible codes. In the example depicted in FIG. 7b, the following codes are chosen: 0011, 0101, 1001 and 1111.

15 In the above examples in which each code is a binary code, each binary "one" represents the existence of a tag and each binary "zero" represents the absence of a tag. When a reaction condition is used in a particular synthesis step, the tags represented by the binary code associated with that reaction condition are also added during that synthesis step. This provides a record of the conditions used during synthesis of a particular library member.

20 For example, assume Reaction Condition 3 (FIG. 5) is used during a first synthesis step, Reaction Condition 1 is used during a second step, and Reaction Condition 6 is used during a third step, then the synthesis code representing the three reaction conditions is 0111 0011 0110. This synthesis code can be read from right to left, in 4-bit blocks, to decode the reaction conditions used during each step of the synthesis. (In another embodiment, the 10 different reaction conditions in FIG. 5 would be alternatives for a single reaction step. A different set of  
25 reaction conditions, encoded by a different set of tags, would be used for the next reaction step.)

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To represent the synthesis code chemically, a set of distinguishable tags is used, in which the presence of a particular tag is represented by a binary "1". In this specific example, twelve (12) bits were used to represent 3 reaction conditions and 3 steps and, thus, a set of twelve tagging molecules are used, T12-T1. T12 represents the leftmost binary bit and T1 represents the rightmost bit of the synthesis code. Therefore, the following tags would represent the 0111 0011 0110 synthesis code: T11, T10, T9, T6, T5, T3 and T2.

The manner in which tagging molecules are prepared and the manner in which tagging molecules relate to the binary bits of a synthesis code, are known in the art and described in various of the above references, each of which has been incorporated herein by reference in its entirety.

When the reaction history of a particular bead is desired, the tags associated with that bead are decoded. In one example, a chromatogram is produced showing peaks where tags are present. From the peaks, a binary code is determined. For instance, in the above example, since a chromatogram would show that T2 and T3 are present and T1 and T4 are absent, the binary code 0110 is provided. This code indicates that Reaction Condition 3 was used during the first synthesis step.

Sometimes the peaks of the chromatogram are not well defined, and thus, it is difficult to determine whether a tag is present. For instance, it is possible that during the tagging reaction, one tag may not be incorporated in a particular bead at the same quantitative level as others within the set. It is also possible that during the detagging/gas chromatograph (GC) portion of the process, some impurities can be introduced into the tag mixture, which may have retention times similar to that of one of the tags in the set. Both of these occurrences can result in chromatogram data in which the tagging code is ambiguous. An example of such is depicted in FIG. 8.

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In the example of FIG. 8, a 5 place binary code is represented. Clearly, tags 5 and 2 are present, while tags 1 and 3 are not. However, because the peak having the retention time in the expected range for tag 4 is of much lower height than either of the other two, its identity is in question. As a result, the binary code, from left to right, can be either 11010 or 10010.

To eliminate this type of ambiguous code reading, the encoding protocol of the present invention is used, in which a specially chosen subset of the N possible binary codes is employed. For example, if a group of codes is selected from the 32 ( $2^5$ ) (see FIG. 6) possible codes, based on a selection criterion of only those codes where the sum of the individual digits is even, then 11010 would not be an acceptable code. Thus, 10010 must be the code that represents the sample depicted in FIG. 8. With this strategy,  $2^{(N-1)}$ -1 unique sets of conditions can be encoded with N tags.

Further examples in which the selective code capability of the present invention is used are depicted in FIGs. 9-10. Each of the figures depicts a sample chromatogram, and each tag within the chromatogram is labelled by CnnCLn. For example, in FIG. 9, peak 900 has tag C12CL5.

In FIG. 9, there is an ambiguity as to whether peak 902 represents the presence of a particular tag or not. Thus, the binary code for that step may be 1101 or 1001. However, based on the criterion for acceptable codes used in this example (e.g., an even number of tags), binary code 1001 (reference number 904) must be the correct code. Therefore, in accordance with the present invention, that peak does not have a tag.

Similarly, in FIG. 10, peak 1000 is in question. However, based on the present invention in which the criterion specifies no single tags, the peak is determined to be tagged. Thus, a binary "one" represents that peak (see reference number 1002). The same holds true for peak 1004.



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The capability of the present invention can readily be automated by creating a suitable program, in software, hardware, microcode, firmware or any combination thereof. Further, any type of computer or computer environment can be employed to provide, incorporate and/or use the capability of the present invention. One such environment is depicted in FIG. 11 and described in detail below.

In one embodiment, a computer environment 1100 includes, for instance, at least one central processing unit 1102, a main storage 1104, and one or more input/output devices 1106, each of which is described below.

As is known, central processing unit 1102 is the controlling center of computer environment 1100 and provides the sequencing and processing facilities for instruction execution, interruption action, timing functions, initial program loading and other machine related functions. The central processing unit executes at least one operating system, which as known, is used to control the operation of the computing unit by controlling the execution of other programs, controlling communication with peripheral devices and controlling use of the computer resources.

Central processing unit 1102 is coupled to main storage 1104, which is directly addressable and provides for high speed processing of data by the central processing unit. Main storage may be either physically integrated with the CPU or constructed in stand alone units.

Main storage 1104 is also coupled to one or more input/output devices 1106. These devices include, for instance, keyboards, communications controllers, teleprocessing devices, printers, magnetic storage media (e.g., tape, disks), direct access storage devices, and sensor based equipment. Data is transferred from main storage 1104 to input/output devices 1106, and from the input/output devices back to main storage.

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Described in detail above is an improvement of the coding process of combinatorial libraries, in which group coding is used. Group coding includes selectively choosing a subset of codes, from N possible codes, that meets one or more predetermined criterion. The subset can include codes that are selected  
5 based on a parity bit or by some other mechanism.

In one example, the code selection capability of the present invention guarantees the presence of enough tag peaks in the chromatogram that, even in the presence of significant variability in the absolute timing of the run, the relative timing can be determined and the "zero" bits identified reliably. The group coding  
10 thus is considered self-clocking.

In one embodiment, the selection capability of the present invention allows more than  $2^{(N-1)}-1$  possibilities for N bits. Further, no bit can be claimed to be merely extraneous to the code. A bit is considered extraneous to the code when the bit is added to the code just for the sake of adding a bit and that bit can really  
15 be ignored when the code is read. With the present invention, these extraneous bits are avoided and thus, more efficient use of tags can be made.

The use of the present invention at each synthesis step can result in avoiding single-bit codes for reaction conditions. Additionally, it advantageously allows for more reliable interpretation of an individual chromatogram by using the  
20 guaranteed presence of a minimum number of tags to create an "internal standard" for the shifts in that chromatogram. Further, it allows for independent error checking of the validity of the tags at each step based on the frequency of the code occurrence and the identification of invalid codes.

Although the examples described above reference binary coding, the  
25 present invention is also applicable to higher order coding or other types of coding. Thus, these are considered a part of the claimed invention.

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- The present invention can be included in an article of manufacture (e.g., one or more computer program products) having, for instance, computer usable media. The media has embodied therein, for instance, computer readable program code means for providing and facilitating the capabilities of the present invention.
- 5 The article of manufacture can be included as a part of a computer system or sold separately.

Additionally, at least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform the capabilities of the present invention can be provided.

- 10 The flow diagrams depicted herein are just exemplary. There may be many variations to these diagrams or the steps (or operations) described therein without departing from the spirit of the invention. For instance, the steps may be performed in a differing order, or steps may be added, deleted or modified. All of these variations are considered a part of the claimed invention.

- 15 Although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the following claims.

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## CLAIMS

What is claimed is:

- 1           1.       A method of determining codes usable in encoding combinatorial  
2       libraries, said method comprising:  
  
3                    selecting a plurality of codes to be assigned to a plurality of  
4       reaction conditions usable during synthesis of a combinatorial library, each  
5       of said plurality of codes comprising a plurality of tags, wherein none of  
6       said plurality of codes comprises only a single tag; and  
  
7                    assigning selected codes to reaction conditions.
- 1           2.       The method of claim 1, wherein each of said plurality of codes is a  
2       binary code, and wherein a binary "one" within said binary code represents the  
3       presence of a particular tag.
- 1           3.       The method of claim 1, wherein said selecting comprises using a  
2       predefined criterion to select said plurality of codes from N possible codes.

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1           4.     The method of claim 3, wherein said predefined criterion specifies  
2     at least one of the following:

3                     each of said plurality of codes includes an even number of tags  
4     present therein;

5                     each of said plurality of codes includes an odd number of tags  
6     present therein, wherein said odd number is greater than one;

7                     each of said plurality of codes includes up to a maximal number of  
8     tags present therein;

9                     each of said plurality of codes includes up to a maximal number of  
10    "zero" bits; and

11                    each of said plurality of codes does not include a predetermined  
12    pattern of bits.

1           5.     The method of claim 1, wherein said selecting comprises using a  
2     parity bit to determine which codes of N possible codes are to be selected as said  
3     plurality of codes.

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1           6.     A method of determining codes usable in encoding chemical  
2 libraries, said method comprising:

3                 selecting, from N possible codes, a group of codes to be assigned  
4 to a plurality of reaction conditions usable during synthesis of a chemical  
5 library, said selecting comprising using a predefined function to select said  
6 group of codes, wherein said predefined function selects fewer than N-1  
7 codes from said N possible codes; and

8                 assigning selected codes to reaction conditions.

1           7.     The method of claim 6, wherein said predefined function specifies  
2 that each code of said group of codes has up to a maximal number of "zero" bits.

1           8.     The method of claim 6, wherein said predefined function specifies  
2 that each code of said group of codes has up to a maximal number of tags.

1           9.     The method of claim 6, wherein said predefined function specifies  
2 that each code of said group of codes has up to a maximal number of "one" bits.

1           10.    The method of claim 6, wherein said predefined function specifies  
2 that each code of said group of codes has an even number of tags present.

1           11.    The method of claim 6, wherein said predefined function specifies  
2 that each code of said group of codes has an odd number of tags present.

1           12.    The method of claim 11, wherein said predefined function specifies  
2 that each code of said group of codes has an odd number, greater than one, of tags  
3 present.

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1           13.    The method of claim 6, wherein said predefined function comprises  
2   not including in said group of codes any code having a predetermined pattern.

1           14.    The method of claim 6, wherein said predefined function comprises  
2   using a parity bit to select said group of codes.

1           15.    The method of claim 6, wherein each of said plurality of codes is a  
2   binary code, and wherein a binary "one" within said binary code represents the  
3   presence of a particular tag.

4           16.    A method of determining codes usable in encoding chemical  
5   libraries, said method comprising:

6                    selecting, from N possible codes, a plurality of codes to be assigned  
7                    to a plurality of reaction conditions usable during synthesis of a chemical  
8                    library, wherein said plurality of codes satisfies a predefined criterion, said  
9                    predefined criterion being other than excluding an "all zeroes" code; and

10                   assigning selected codes to reaction conditions.

1           17.    The method of claim 16, wherein each of said plurality of codes is a  
2   binary code, and wherein a binary "one" within said binary code represents the  
3   presence of a particular tag.

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1           18.    The method of claim 16, wherein said predefined criterion specifies  
2   at least one of the following:

3                   each of said plurality of codes includes an even number of tags  
4           present therein;

5                   each of said plurality of codes includes an odd number of tags  
6           present therein;

7                   each of said plurality of codes includes up to a maximal number of  
8           tags present therein;

9                   each of said plurality of codes includes up to a maximal number of  
10       "zero" bits; and

11                   each of said plurality of codes does not include a predetermined  
12       pattern of bits.

1           19.    The method of claim 16, wherein said selecting comprises using a  
2   parity bit to determine which codes of N possible codes are to be selected as said  
3   plurality of codes.



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1           20.     A system of determining codes usable in encoding combinatorial  
2 libraries, said system comprising:

3                     means for selecting a plurality of codes to be assigned to a plurality  
4 of reaction conditions usable during synthesis of a combinatorial library,  
5 each of said plurality of codes comprising a plurality of tags, wherein none  
6 of said plurality of codes comprises only a single tag; and

7                     means for assigning selected codes to reaction conditions.

1           21.     The system of claim 20, wherein said means for selecting comprises  
2 means for using a predefined criterion to select said plurality of codes from N  
3 possible codes.

1           22.     A system of determining codes usable in encoding chemical  
2 libraries, said system comprising:

3                     means for selecting, from N possible codes, a group of codes to be  
4 assigned to a plurality of reaction conditions usable during synthesis of a  
5 chemical library, said means for selecting comprising means for using a  
6 predefined function to select said group of codes, wherein said predefined  
7 function selects fewer than N-1 codes from said N possible codes; and

8                     means for assigning selected codes to reaction conditions.

1           23.     The system of claim 22, wherein said predefined function specifies  
2 that each code of said group of codes has up to a maximal number of "zero" bits.

1           24.     The system of claim 22, wherein said predefined function specifies  
2 that each code of said group of codes has up to a maximal number of tags.

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1           25.    The system of claim 22, wherein said predefined function specifies  
2   that each code of said group of codes has an even number of tags present.

1           26.    The system of claim 22, wherein said predefined function specifies  
2   that each code of said group of codes has an odd number of tags present.

1           27.    The system of claim 22, wherein said predefined function comprises  
2   not including in said group of codes any code having a predetermined pattern.

1           28.    The system of claim 22, wherein said predefined function comprises  
2   using a parity bit to select said group of codes.

1           29.    A system of determining codes usable in encoding chemical  
2   libraries, said system comprising:

3                   means for selecting, from N possible codes, a plurality of codes to  
4   be assigned to a plurality of reaction conditions usable during synthesis of a  
5   chemical library, wherein said plurality of codes satisfies a predefined  
6   criterion, said predefined criterion being other than excluding an "all  
7   zeroes" code; and

8                   means for assigning selected codes to reaction conditions.

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1           30.    The system of claim 29, wherein said predefined criterion specifies  
2   at least one of the following:

3                   each of said plurality of codes includes an even number of tags  
4   present therein;

5                   each of said plurality of codes includes an odd number of tags  
6   present therein;

7                   each of said plurality of codes includes up to a maximal number of  
8   tags present therein;

9                   each of said plurality of codes includes up to a maximal number of  
10   "zero" bits; and

11                   each of said plurality of codes does not include a predetermined  
12   pattern of bits.

1           31.    The system of claim 29, wherein said means for selecting comprises  
2   means for using a parity bit to determine which codes of N possible codes are to  
3   be selected as said plurality of codes.

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1           32.    An article of manufacture, comprising:

2                   at least one computer usable medium having computer readable program  
3 code means embodied therein for causing the determining of codes usable in  
4 encoding combinatorial libraries, the computer readable program code means in  
5 said article of manufacture comprising:

6                   computer readable program code means for causing a computer to  
7 select a plurality of codes to be assigned to a plurality of reaction  
8 conditions usable during synthesis of a combinatorial library, each of said  
9 plurality of codes comprising a plurality of tags, wherein none of said  
10 plurality of codes comprises only a single tag; and

11                  computer readable program code means for causing a computer to  
12 assign selected codes to reaction conditions.

1           33.    At least one program storage device readable by a machine,  
2 tangibly embodying at least one program of instructions executable by the machine  
3 to perform a method of determining codes usable in encoding chemical libraries,  
4 said method comprising:

5                   selecting, from N possible codes, a group of codes to be assigned  
6 to a plurality of reaction conditions usable during synthesis of a chemical  
7 library, said selecting comprising using a predefined function to select said  
8 group of codes, wherein said predefined function selects fewer than N-1  
9 codes from said N possible codes; and

10                  assigning selected codes to reaction conditions.

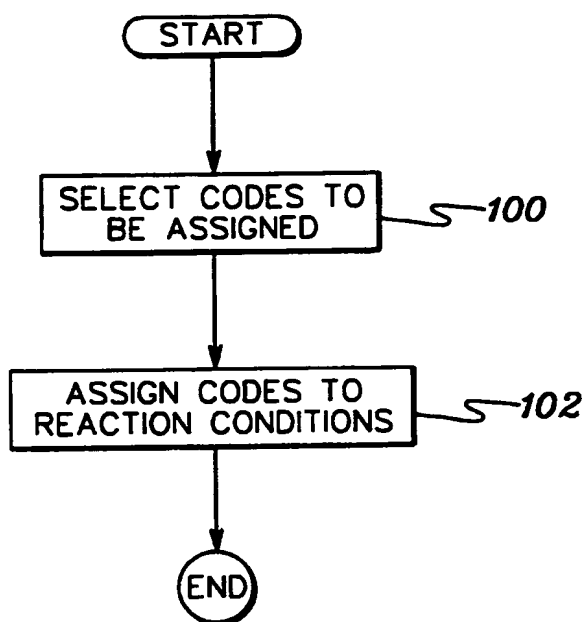
-27-

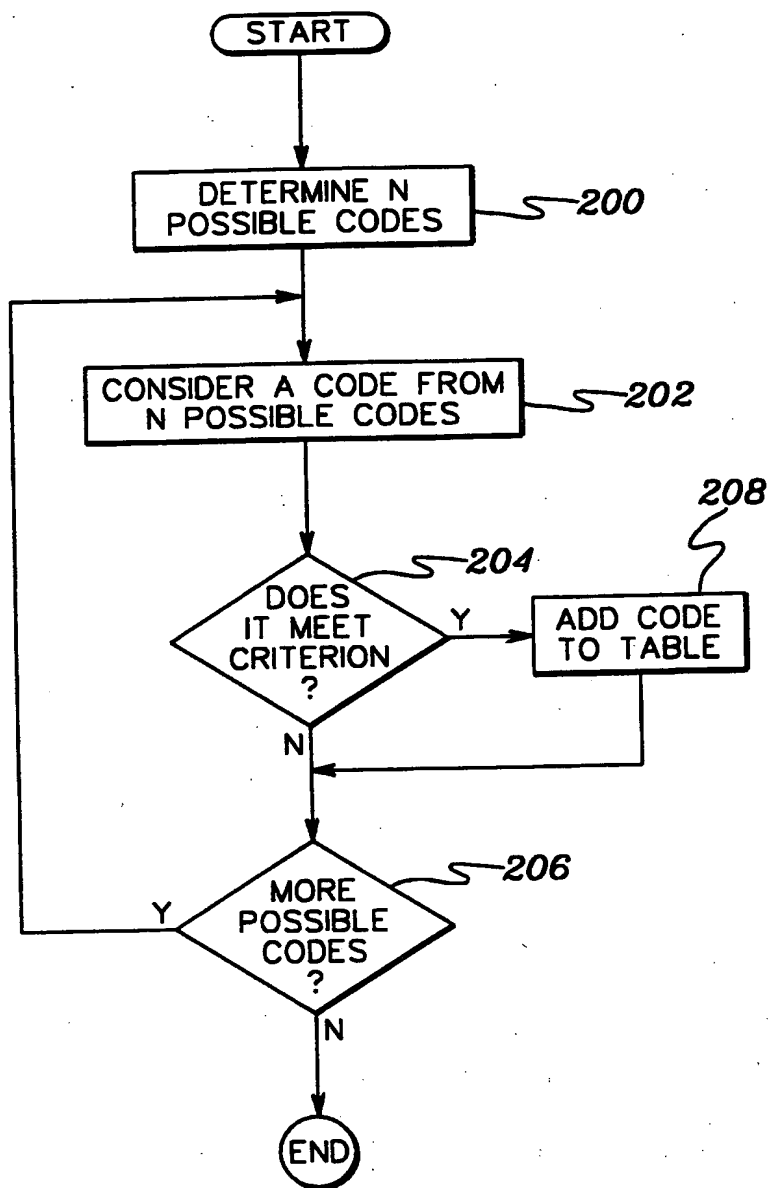
1           34.    At least one program storage device readable by a machine,  
2 tangibly embodying at least one program of instructions executable by the machine  
3 to perform a method of determining codes usable in encoding chemical libraries,  
4 said method comprising:

5                   selecting, from N possible codes, a plurality of codes to be assigned  
6 to a plurality of reaction conditions usable during synthesis of a chemical  
7 library, wherein said plurality of codes satisfies a predefined criterion, said  
8 predefined criterion being other than excluding an "all zeroes" code; and

9                   assigning selected codes to reaction conditions.

\* \* \* \* \*

*fig. 1*

*fig. 2*

## N POSSIBLE CODES

0000	1000
0001	1001
0010	1010
0011	1011
0100	1100
0101	1101
0110	1110
0111	1111

*fig. 3*

## TABLE OF ACCEPTED CODES

CODE	REACTION CONDITION
0011	
0101	
0110	
1001	
1100	
0111	
1011	
1101	
1110	
1111	

*fig. 4*



TABLE OF ACCEPTED CODES

CODE	REACTION CONDITION
0011	CONDITION 1
0101	CONDITION 2
0110	CONDITION 3
1001	CONDITION 4
1100	CONDITION 5
0111	CONDITION 6
1011	CONDITION 7
1101	CONDITION 8
1110	CONDITION 9
1111	CONDITION 10

*fig. 5*

0	0	0	0	0	NOT USED
0	0	0	0	1	NOT USED
0	0	0	1	0	NOT USED
0	0	0	1	1	USED
0	0	1	0	0	NOT USED
0	0	1	0	1	USED
0	0	1	1	0	USED
0	0	1	1	1	NOT USED
0	1	0	0	0	NOT USED
0	1	0	0	1	USED
0	1	0	1	0	USED
0	1	0	1	1	NOT USED
0	1	1	0	0	USED
0	1	1	0	1	NOT USED
0	1	1	1	0	NOT USED
0	1	1	1	1	USED
1	0	0	0	0	NOT USED
1	0	0	0	1	USED
1	0	0	1	0	USED
1	0	0	1	1	NOT USED
1	0	1	0	0	USED
1	0	1	0	1	NOT USED
1	0	1	1	0	NOT USED
1	0	1	1	1	USED
1	1	0	0	0	USED
1	1	0	0	1	NOT USED
1	1	0	1	0	NOT USED
1	1	0	1	1	USED
1	1	1	0	0	USED
1	1	1	0	1	NOT USED
1	1	1	1	0	NOT USED
1	1	1	1	1	USED
1	1	1	1	0	USED
1	1	1	1	1	NOT USED

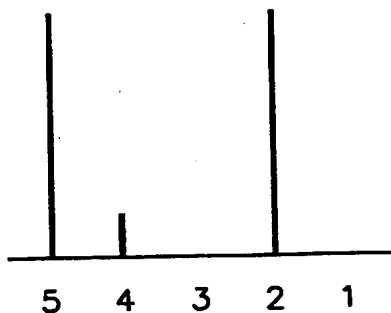
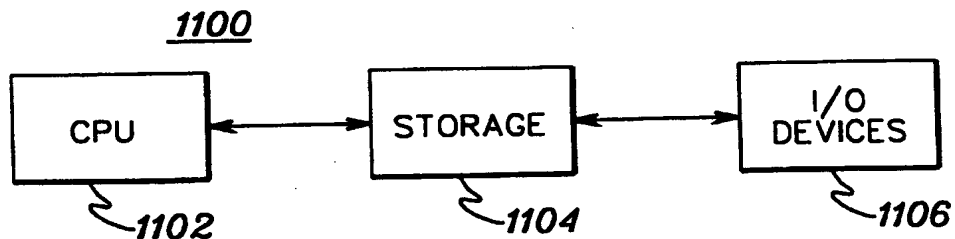
*fig. 6*

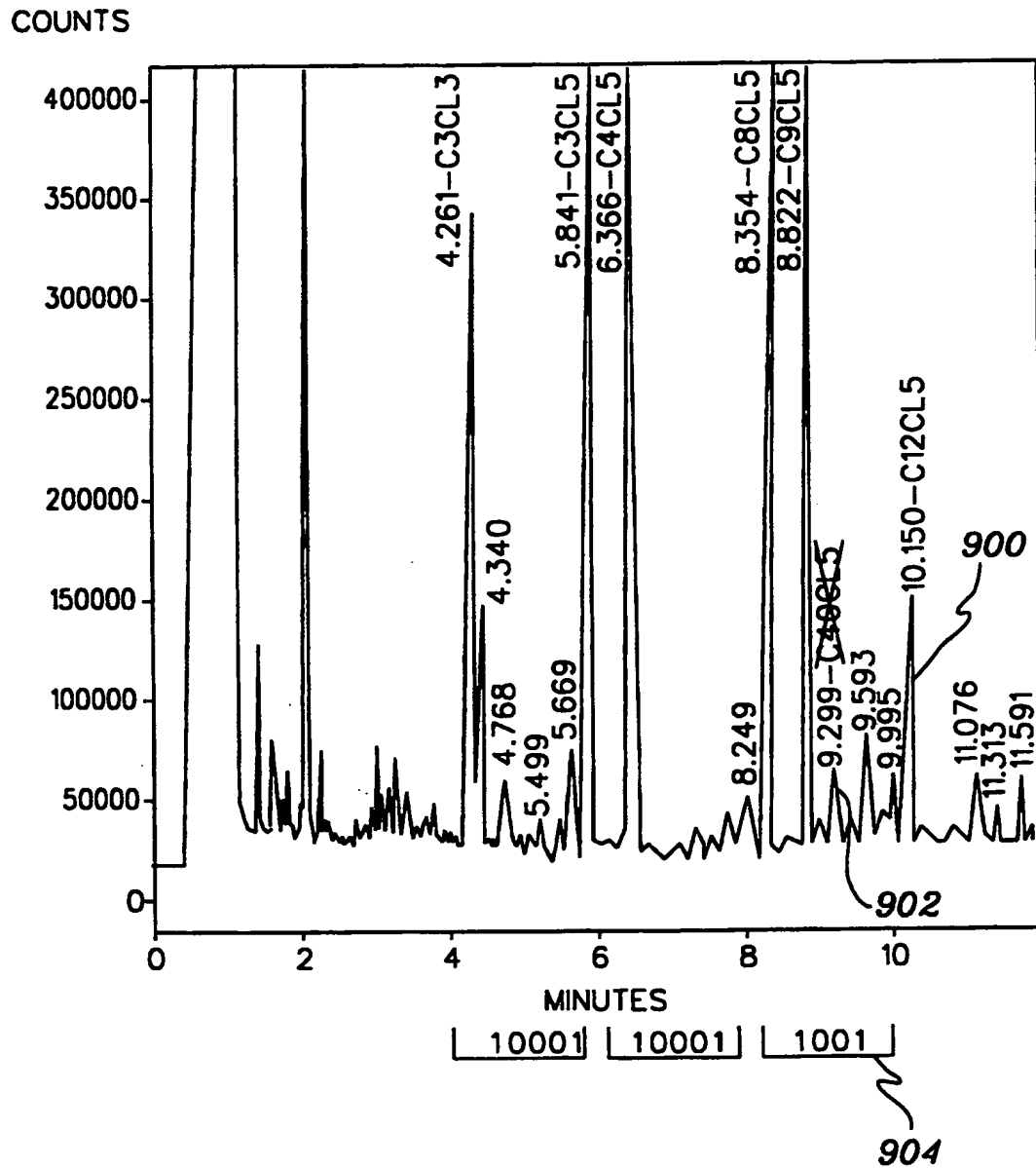
POSSIBLE CODES

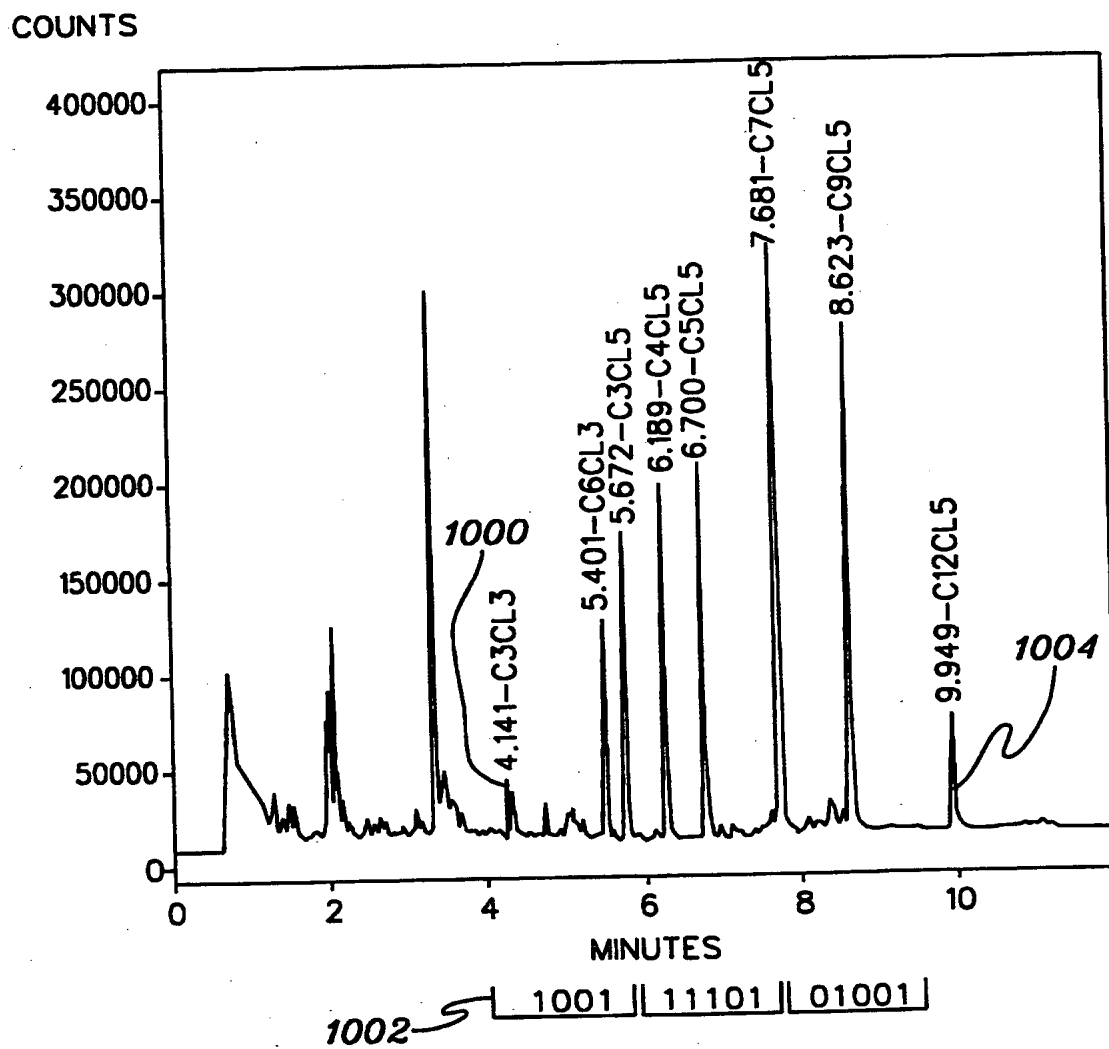
000
001
010
011
100
101
110
111

*fig. 7a*

CODE	PARITY
000	0
001	1
010	1
011	0
100	1
101	0
110	0
111	1

*fig. 7b**fig. 8**fig. 11*

*fig. 9*

*fig. 10*

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- (71) Applicant: PHARMACOEPIA, INC. [US/US]; 3000 Eastpark Boulevard, Cranbury, NJ 08512 (US).
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- (88) Date of publication of the international search report:  
4 January 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 00/21909 A3

(54) Title: SELECTING CODES TO BE USED FOR ENCODING COMBINATORIAL LIBRARIES

(57) Abstract: Codes to be used for encoding combinatorial libraries are selectively chosen based on one or more predefined function or criterion. In particular, a subset of N possible codes is selected based on some criterion. In one example, the codes are binary codes, and each code represents the tags used during a particular stage of synthesis of members of a combinatorial library. The tags define the reaction condition used during that particular stage of synthesis. In one embodiment, the predefined criterion ensures that each code includes more than one tag. This helps eliminate ambiguity during a decoding process in which the tags are identified to determine the reaction history during synthesis.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/23444

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07B61/00 G06F19/00 B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEBL M. ET AL.: "One-bead-one-structure combinatorial libraries" BIOPOLYMERS (PEPTIDE SCIENCE), vol. 37, 1995, pages 177-198, XP000929745 page 187, right-hand column -page 189, left-hand column figure 12 --- -/-	1,20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 August 2000

Date of mailing of the international search report

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Held, P

# INTERNATIONAL SEARCH REPORT

Int. Patent Application No  
PCT/US 99/23444

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>OHLMEYER M H J ET AL: "COMPLEX SYNTHETIC CHEMICAL LIBRARIES INDEXED WITH MOLECULAR TAGS"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, US, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 90, 1 December 1993 (1993-12-01), pages 10922-10926, XP000652270 ISSN: 0027-8424 cited in the application page 10923, right-hand column, last paragraph -page 10924, left-hand column</p>	1,6,16, 20,22,29
A	<p>WO 95 28640 A (READER JOHN C ;STILL W CLARK (US); UNIV COLUMBIA (US); COLD SPRING) 26 October 1995 (1995-10-26) claim 1</p>	1,6,16, 20,22,29
A	<p>CHABALA J C ET AL: "BINARY ENCODED SMALL-MOLECULE LIBRARIES IN DRUG DISCOVERY AND OPTIMIZATION"</p> <p>PERSPECTIVES IN DRUG DISCOVERY AND DESIGN, XX, ESCOM SCIENCE PUBLISHERS BV, vol. 2, 1994, pages 305-318, XP000654519 ISSN: 0928-2866 page 307, paragraph 4 -page 313, paragraph 3</p>	1,6,16, 20,22,29
A	<p>BALDWIN J J ET AL: "SYNTHESIS OF A SMALL MOLECULE COMBINATORIAL LIBRARY ENCODED WITH MOLECULAR TAGS"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 117, no. 20, 1995, pages 5588-5589, XP000652265 ISSN: 0002-7863 the whole document</p>	1,6,16, 20,22,29



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23444

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9528640 A	26-10-1995	US 5565324 A	15-10-1996
		AU 2292695 A	10-11-1995
		CA 2187792 A	26-10-1995
		CN 1151793 A	11-06-1997
		EP 0755514 A	29-01-1997
		HU 74985 A	28-03-1997
		JP 10502614 T	10-03-1998
		NO 964332 A	03-12-1996
		US 5968736 A	19-10-1999
		US 6001579 A	14-12-1999
		US 5789172 A	04-08-1998

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